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*Editorial Comment*

# Atrial Natriuretic Factor: A Ventricular Hormone?*

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The adaptive mechanisms of the heart to chronic ventricular overload have recently been reviewed (1). They include ventricular hypertrophy; molecular changes in contractile proteins, particularly the synthesis of fetal myosin isoforms (2,3); and a complex reprogramming of cardiac gene expression (4). Experimental data also provide evidence of ventricular activation of the atrial natriuretic factor (ANF) gene (5–9). Children with congenital heart disease provide hemodynamic models of pressure and volume overload, allowing the study of the contribution of the atria and the ventricles to ANF production.

**Current study.** In the current issue of the Journal, Oberhänsli et al. (10) report the ANF plasma concentrations and hemodynamic variables obtained from sequential measurements from the inferior vena cava to the pulmonary artery, as well as from the left atrium and the aorta, in young patients with three types of conditions. Patients with tetralogy of Fallot, that is, with right ventricular pressure overload, constituted group I; patients with left to right shunt lesions and pulmonary hypertension, that is, with ventricular volume overload and a variable degree of right ventricular pressure overload, constituted group II; and patients with minor cardiac abnormalities constituted the control group. Group II patients had significant enlargement of the left atrium compared with that in the other two groups; these children had significantly higher ANF levels and were well separated from the control group but less well from those with tetralogy of Fallot. In groups I and II there was a 50% increase in ANF concentrations from the inferior vena cava to the right atrium and a further 30% increase from the right atrium to the pulmonary artery. Clearly, the distension of the left atrium present in the group II patients but not in the patients with tetralogy of Fallot must account for a significant part of the difference in ANF released. Is it, however, the only explanation of the difference? In group I (patients with right ventricular pressure overload and a normal-sized left atrium) plasma levels of ANF tend to be increased because of right atrial and probably right ventricular contributions, but the increase is slight and variable. In group II (a less homogeneous group of patients with a variable degree of right ventricular pressure overload and a significant left ventricular volume overload, as indicated by an enlarged left atrium and possibly a right ventricular volume overload in some patients) ANF elevation is significant and results presumably from contributions of the right and left atria, and also from the right and left ventricles.

To test further the potential contribution of the right ventricle, the authors (10) induced a temporary right ventricular volume and pressure overload, which also resulted in an increase in right atrial pressure. They observed an increase in ANF levels between the right atrium and the pulmonary artery in all groups, suggesting to the authors the existence of a ventricular site for the production and release of the hormone.

Several issues raised by this elegant study need to be addressed: 1) Can the conclusion that there is a ventricular contribution to ANF release be accepted without data from various sites in the coronary sinus system? 2) What is the significance and role of ventricular ANF? 3) What are the differences between atrial and ventricular ANF? 4) What are the clinical implications of plasma ANF increases in compensated congenital heart disease?

**1. Is there a ventricular contribution to plasma ANF?** The significant increases in ANF levels between the inferior vena cava and the right atrium and then between the right atrium and the pulmonary artery suggest a significant contribution by the blood from the coronary sinus. However, because only one sample was taken in the right atrium, none in the right ventricle and none in the coronary sinus system, uncertainty persists about the precise origin of the hormone sampled in the right atrium and the pulmonary artery.

However, because the anatomy of the venous drainage of the heart has now been clarified (11) and demonstrated angiographically (12) in the conscious adult human being, it may in some instances be possible to document the origin of ANF by selective blood sampling in the coronary sinus system. The coronary sinus is the common terminal portion of a number of variably developed veins. Its main tributaries are the great cardiac vein, the posterior interventricular vein, the posterior vein of the left ventricle, the oblique vein of Marshall and the small cardiac vein (11). The anterior interventricular vein which is situated in the anterior interventricular groove and is upstream of the great cardiac vein, drains blood from the left ventricle but not from the atria (13). Yasue et al. (13) have been able to document the release

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of ANF from the left ventricle in patients with dilated cardiomyopathy by sampling blood for ANF levels from the aorta, the coronary sinus, the great cardiac vein and the anterior interventricular vein. There was a significant increase in plasma ANF levels between the root of the aorta and the anterior interventricular vein, and this correlated well with impairment of left ventricular function (13). Although admittedly difficult to accomplish in children with congenital heart disease, in whom anatomic variations might occur, similar sampling could confirm or exclude the contribution of the left ventricle.

Venous drainage of the lateral wall of the right ventricle occurs through the small cardiac vein and the right marginal vein, which most often join to empty either into the coronary sinus or directly into the right atrial cavity. The anterior portion of the right ventricle drains through the anterior cardiac vein, which empties directly into the right atrium or may join the anterior interventricular vein (12). Selective sampling of the drainage from the right ventricle might be nearly impossible, because in only 25% of patients does the small cardiac vein flow either directly into the coronary sinus or enter it through a short portion of the posterior interventricular vein (11). Ventricular biopsies may help demonstrate conclusively the contribution of the ventricles to ANF release.

The oblique vein of Marshall, which joins the great cardiac vein to form the coronary sinus, is the principal drainage vessel for left atrial venous blood. The left posterior atrial veins also drain the left atrium and empty into the coronary sinus. Venous drainage may also occur directly into the left atrial cavity through the thebesian veins (14); however, these veins are present only to a small and variable extent in the left atrium (15). Catheterization of the oblique vein of Marshall to explore ANF release by the left atrium, although theoretically possible, has not been reported.

The primary means of drainage of right atrial wall blood is still controversial. Part of the blood drains through the small cardiac vein, which joins the proximal coronary sinus or empties directly into the atrial cavity. In addition, a significant fraction of venous blood is thought to drain directly into the lumen of the right atrium through the thebesian veins (16).

**2. Reinduction of ventricular ANF gene in ventricular hypertrophy: significance and role of ventricular ANF.** During fetal development in rats ANF messenger ribonucleic acid (mRNA) concentrations are similar in the atria and ventricles (17,18), but these concentrations decrease precipitously in the ventricles after birth, reaching levels that are at least 10 times lower than those in the atria of adult rats (19). The decrease of ANF messenger ribonucleic acid (RNA) and peptide from ventricular muscle may reflect a tissue-specific inactivation of the ANF gene after cessation of cardiac cell growth. However, a number of conditions are now known to produce an elevation of both immunoreactive ANF and ANF messenger RNA levels in the adult ventricles, both in vivo and in vitro (4,5,20–25). A pronounced elevation of ventricular ANF messenger RNA and immunoreactive ANF levels has been shown to be associated with ventricular hypertrophy in volume-overloaded rats (5,21). Likewise, in hamsters with cardiomyopathy an increase in ANF messenger RNA and peptide occurs when compensatory cardiac hypertrophy develops, and the increase takes place before the hemodynamic changes observed in heart failure (20,22,23).

In persons with normal cardiovascular hemodynamics, the ANF gene is expressed in both the ventricles and the atria, but the concentration in the ventricles appears very low. With the occurrence of heart failure, there is an increase in both atrial and ventricular ANF gene expression (26,27). Saito et al. (27) found that in patients with dilated cardiomyopathy or with a previous myocardial infarction, ANF levels were increased by two or three times in the atria compared with levels in normal control subjects, whereas the levels in the ventricles were 40 times higher than those of control subjects. ANF messenger RNA levels in the ventricles of such patients showed a 10-fold increase compared with levels in normal ventricles, and the total content in the ventricles reached about 30% of that in the atria of the same heart.

Thus, these data suggest that the expression of the ANF gene is reinduced in the ventricles of patients with congestive heart failure (27). Furthermore, in keeping with experimental data (13,28) that indicate that the expression of the ANF gene is markedly increased in ventricles of spontaneously hypertensive rats and stroke-prone spontaneously hypertensive rats with ventricular hypertrophy, the data of Oberhänsli et al. (10) suggest that a reinduction of the ANF gene may also occur in compensated congenital heart disease with ventricular overload and some degree of ventricular hypertrophy.

**3. Differences between atrial and ventricular ANF.** Bloch et al. (18) have shown that in tissues and in primary cultures, the neonatal atrial and ventricular cardiocytes differed in their storage of ANF. Ventricular cardiocytes stored little ANF, whereas atrial cardiocytes appeared to store the propeptide of ANF. Thus, atrial and ventricular cardiocytes may release ANF in different ways. Atrial cardiocytes secrete ANF by means of a regulated pathway, because they store ANF, contain abundant secretory granules and appear to respond to appropriate stimuli. In contrast, neonatal ventricular cardiocytes appear to use a constitutive pathway for ANF secretion, and they release ANF rapidly after synthesis. Theoretically, therefore, an acute increase in volume or pressure overload probably does not affect the level of ventricular ANF secretion.

**4. Clinical implications of increased ventricular ANF gene expression in compensated congenital heart disease.** It appears that in children with compensated heart disease, all four chambers of the heart may, as in the rat (5), express the ANF gene under conditions of pressure or volume overload. Then, the human heart with ventricular hypertrophy, like the hamster heart, may return to a fetal or neonatal type of ANF secretion; the amount of ventricular immunoreactive ANF

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and ANF messenger RNA increases, and typical secretory granules appear in approximately 20% of ventricular cardiocytes. The increased ventricular ANF secretion may help buffer the neurohormonal effects of congestive heart failure. As congestive heart failure develops, the atrial contribution to immunoreactive ANF production and total ANF messenger RNA content appears to decrease, while the ventricles appear to take over the production of ANF. In severe congestive heart failure in the hamster, for instance, as much as 74% of circulating ANF is produced in the ventricles. Finally, the ratio of immunoreactive ANF levels to ANF messenger RNA levels in the ventricles is much smaller than that in the atria. This suggests a more rapid secretion of ANF after synthesis in the ventricles and is consistent with a constitutive type of secretion of immunoreactive ANF from the ventricular cardiocytes (18).

**Conclusions.** Thus, these clinical data provide indirect support for the experimental studies that have suggested that *ANF gene reprogramming* may occur at the onset of ventricular hypertrophy (5–9). In conjunction with other changes involving in particular the adrenergic nervous system, the aldosterone-renin-angiotensin system and the vasopressin system, this may help prevent or delay the occurrence of congestive heart failure. Clearly, additional research is needed to document better in the young and in adults the ventricular origin of ANF and to understand better both the regulation of its ventricular release and the mechanism of induction of the ventricular ANF gene, so that therapeutic applications may be developed.

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## References

1. Katz AM. Cardiomyopathy of overload. N Engl J Med 1990;322:100–10.
2. Schiaffino S, Samuel JL, Sassoon D, et al. Uncoordinated accumulation of α-skeletal actin and β-myosin heavy chain mRNAs during early stages of pressure overload-induced cardiac hypertrophy demonstrated by in situ hybridization. Circ Res 1989;64:937–48.
3. Izumo SA, Lompré AM, Matsuoka R, et al. Myosin heavy chain messenger RNA and protein isoform transitions during cardiac hypertrophy: interaction between hemodynamic and thyroid hormone-induced signals. J Clin Invest 1987;79:970–7.
4. Izumo S, Nadal-Ginard B, Mahdavi V. Protooncogene induction and reprogramming of cardiac gene expression produced by pressure overload. Proc Natl Acad Sci USA 1988;85:339–43.
5. Lattion AL, Michel JB, Arnauld E, Corvol P, Soubrier F. Myocardial recruitment during ANF mRNA increase with volume overload in the rat. Am J Physiol 1986;251:H890–6.
6. Mercadier JJ, Lompré AM, de la Bastie D, Wisnewsky C, Schwartz K. Left ventricular accumulation of messenger ribonucleic acid of atrial natriuretic factor in the rat at the compensatory stage of pressure overload induced cardiac hypertrophy. CR Acad Sci Ser III 1987;305:79–82.
7. Lee RT, Bloch KD, Pfeffer JM, Pfeffer MA, Neer EJ, Seidman CE. Atrial natriuretic factor gene expression in ventricles of rats with spontaneous biventricular hypertrophy. J Clin Invest 1988;81:431–4.
8. Mercadier JJ, Samuel JL, Michel JB, et al. Atrial natriuretic factor gene expression in rat ventricle during experimental hypertension. Am J Physiol 1989:257:H979–87.
9. Thibault G, Nemer M, Drouin J, et al. Ventricles as a major site of atrial natriuretic factor synthesis and release in cardiomyopathic hamster with heart failure. Circ Res 1989;65:71–82.
10. Oberhänsli I, Mermillod B, Favre H, Friedli B, Girardin E, Paunier L. Atrial natriuretic factor in patients with congenital heart disease; correlation with hemodynamic variables. J Am Coll Cardiol 1990;15:1438–45.
11. Tschabitscher M. Anatomy of coronary veins. In: Mohl W, Wolner E, Glogar D, eds. The Coronary Sinus: Proceedings of the 1st International Symposium on Myocardial Protection Via the Coronary Sinus. Darmstadt: Steinkopff Verlag; New York: Springer-Verlag, 1984:8–25.
12. Gensini GG, Giorgi SD, Coskun O, Palacio A. Anatomy of the coronary circulation in living man: coronary venography. Circulation 1965;31:778–84.
13. Yasue H, Obata K, Okumura K, et al. Increased secretion of atrial natriuretic polypeptide from the left ventricle in patients with dilated cardiomyopathy. J Clin Invest 1989;83:46–51.
14. Butterworth RF. The venous drainage of the left atrium. J Anat 1954;88: 131–3.
15. Williams PL, Warwick R, eds. Gray's Anatomy. 36th ed. London: Churchill Livingstone, 1980:732–8.
16. Little RC. Physiology of the Heart and Circulation. 3rd ed. Chicago: Year Book Medical, 1985:39.
17. Wei Y, Rodi CP, Day ML, et al. Developmental changes in the rat atriopeptin hormonal septum. J Clin Invest 1987;79:1325–9.
18. Bloch KD, Seidman JC, Naftilan JD, Fallon JT, Seidman CE. Neonatal atria and ventricles secrete atrial natriuretic factor via tissue-specific secretory pathways. Cell 1986;47:695–702.
19. Nemer M, Lavigne JP, Drouin J, Thibault G, Gannong G, Antakly T. Expression of atrial natriuretic factor gene in heart ventricular tissue. Peptides 1986;7:1147–52.
20. Thibault G, Nemer M, Drouin J, et al. Ventricles as a major site of atrial natriuretic factor synthesis and release in cardiomyopathic hamster with heart failure. Circ Res 1989;65:71–82.
21. Day ML, Schwartz D, Wiegand RC, et al. Ventricular atriopeptin: unmasking of messenger RNA and peptide synthesis by hypertrophy or dexamethasone. Hypertension 1987;9:485–91.
22. Ding J, Thibault G, Gutkowska J, et al. Cardiac and plasma atrial natriuretic factor (ANF) in experimental congestive heart failure. Endocrinology 1987;121:248–57.
23. Cantin M, Thibault G, Ding J, et al. ANF in experimental congestive heart failure. Am J Pathol 1988;130:552–68.
24. Arai H, Nakao K, Saito Y, et al. Augmented expression of atrial natriuretic polypeptide (ANP) in ventricles of spontaneously hypertensive rats (SHR) and SHR-stroke prone. Circ Res 1988;62:926–30.
25. Takayanagi R, Imada T, Inagami T. Synthesis and presence of atrial natriuretic factor in rat ventricles. Biochem Biophys Res Commun 1987:142:483–8.
26. Sugawara A, Nakao K, Morii N, et al. Synthesis of atrial natriuretic polypeptide (ANP) in human failing hearts: evidence for altered processing of ANP precursor and augmented synthesis of β-human ANP. J Clin Invest 1988;81:1962–70.
27. Saito Y, Nakao K, Arai H, et al. Atrial natriuretic polypeptide (ANP) in human ventricle: increased gene expression of ANF in dilated cardiomyopathy. Biochem Biophys Res Commun 1987;148:211–7.
28. Arai H, Nakao K, Saito Y, et al. Simultaneous measurement of atrial natriuretic polypeptide (ANP) messenger RNA and ANP in rat heart: evidence for a preferentially increased synthesis and secretion of ANP in left atrium of spontaneously hypertensive rats (SHR). Biochem Biophys Res Commun 1987;148:239–45.